INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2004/000977

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-48 as originally filed

   Sequence listings part of the description, Pages

   1-11 as originally filed

   Claims, Numbers

   1-61 as originally filed

   Drawings, Sheets

   1-7 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2004/000977

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-41,59-61

because:

☒ the said international application, or the said claims Nos. 1-41 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 8-9,59-61 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 8-9,59-61 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2004/000977

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-7,13-23,26-41,49-58
	No:	Claims	1-2,10-12,24-25,42-48
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7,10-58
Industrial applicability (IA)	Yes:	Claims	42-61 (YES), 1-41 see separate sheet
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2004/000977

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

1. Reference is made to the following documents :

D1: WO 01/10383 A (VERTEX PHARMACEUTICALS INCORPORATED; GOLEC, JULIAN; CHARIFSON, PAUL; B) 15 February 2001 (2001-02-15)

D2: WO 01/94351 A (VERTEX PHARMACEUTICALS INCORPORATED; CHARRIER, JEAN-DAMIEN; BRENCHLEY,) 13 December 2001 (2001-12-13)

D3: US 2003/083296 A1 (ZHANG HONG ET AL) 1 May 2003 (2003-05-01)

D4: WO 99/25832 A (THE BOARD OF TRUSTEES OF LELAND STANFORD JUNIOR UNIVERSITY) 27 May 1999 (1999-05-27)

D5: WO 03/020767 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD; WALLACH, DAVID; GONCHAROV, TANY) 13 March 2003 (2003-03-13)

D6: VARFOLOMEEV E.E. ET AL.: "Targeted disruption of the mouse caspase 8 gene ablates cell death induction by the TNF receptors, Fas/Apo1, and DR3 is lethal prenatally." IMMUNITY, vol. 9, August 1998 (1998-08), pages 267-276, XP002320053

D7: SALMENA L. ET AL.: "Essential role for caspase-8 in T cell homeostasis and T cell mediated immunity." GENES AND DEVELOPMENT, vol. 17, 21 March 2003 (2003-03-21), pages 883-895, XP002320054

D8: KENNEDY N.J. ET AL.: "Caspase activation is required for T cell proliferation." J. EXP. MED., vol. 190, no. 12, 20 December 1999 (1999-12-20), pages 1891-1895, XP002320055

D9: CHLICHLIA K. ET AL.: "Caspase activation is required for nitric oxide-mediated CD95 (Apo1/Fas)-dependent and independent apopotosis in human neoplastic lymphoid cells." BLOOD, vol. 91, no. 11, 1 June 1998 (1998-06-01), pages 4311-4320, XP002320056

D10: WANG J. AND LENARDO M.J.: "Roles of caspases in apoptosis, development and cytokine maturation revealed by homozygous gene deficiencies." J. CELL SCIENCE, vol. 113, 2000, pages 753-757, XP002320057

Unless specified otherwise, the relevant passages are the ones that are cited in the Search Report.

Regarding point III

2. Claims 1-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Regarding point V

3. For the assessment of the present claims 1-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. The treatment of hematopoietic diseases or leukemias is encompassed within the scope of claim 1. All of D1-D4 disclose the use of caspase-8 inhibitors for treating leukemia or hematopoietic disorders. Claims 1-2, 10-12, 24-25 and 45-48 are not novel.

4.1 Claim 42 is drafted as a kit claim but does not contain any acceptable limiting technical feature ("identified for use..." is not limiting) except for a packaging material and a composition containing an inhibitor of caspase-8.
Since compositions are always in some kind of container or packaging, claims 42-44 are anticipated by all of D1-D5.

4.2 No document was found that discloses an antisense or a siRNA having the sequences of Seq. ID No.15 and 16. Claims 3,7,13,17,26,30,33,37,49 and 53 are

novel.

4.3 The use of the specific caspase-8 inhibitors recited in claim 6 for the manufacture of a medicament for treating leukemia or other hematopoietic diseases is not described in the prior art. Claims 6,16,29,36 and 52 are new.

4.4 The combined use of a caspase-8 inhibitor and chemotherapy, radiotherapy, bone marrow transplantation or a growth factor has not been disclosed previously. Claims 18-23, 31-32, 38-41 and 54-58 are novel.

5. The technical problem solved by the application is to provide a therapeutic agent for treating hematopoietic diseases, preferably leukemias.
The solution to the problem is the use of inhibitors of caspase-8.
As a support to this "invention", the application provides the following supporting data:
conditional caspase-8 knockout mice were generated and a phenotype of impaired hematopoiesis and impaired immune response was observed. No experiment was actually carried out with caspase-8 inhibitor(s).
Either D6 or D7 can be regarded as the closest prior art. D6 shows that hematopoiesis is impaired in caspase-8 knockout mouse embryos. In D7, mice carry a caspase-8 knockout mutation but only in T cell lineages. The phenotype of these mice is a reduced number of T cells and impaired immune response.
It follows that the application does not show more than what was already known in the art ; the fact that caspase-8 plays an important role in hematopoiesis is only confirmed. In addition, the use of caspase-8 inhibitors for modulating hematopoiesis remains completely speculative (at least as far as the present application is concerned) since there is no single working example of a use of a caspase-8 inhibitor in the application. The role of caspase-8 in hematopoiesis was already established in the prior art (see D6 and D7, and also the review article D10 dated 2000). The use of known caspase inhibitors for treating leukemia or hematopoietic diseases is already claimed in D1-D4. In conclusion, the application does not show any technical effect that is sufficient to be entitled to the protection that would be granted by the present claims.

Concerning combination therapy (with chemotherapy, bone marrow transplantation etc...) : no evidence or supporting data are given regarding these embodiments. Since no technical effect is shown, these features (although novel) cannot grant an inventive step.
Regarding specific inhibitors such as , for example, the antisense or siRNA having Seq. No.15 or 16 : the same arguments apply.

In conclusion, claims 1-7 and 10-58 are not inventive.

Regarding point VIII

6. Claims 8-9 and 59-61 relate to all peptides that inhibit the caspase-8 signalling pathway (meaning almost all caspases plus other proteins). These claims are not clear because they encompass an enormous number of potential compounds. These claims are not fully supported by the description either: the only compounds that are actually disclosed are caspase-8 inhibitors.
No further opinion is given on these claims.

6.1 The whole application is not clear because it lacks conciseness : there are too many independent claims, some of which being specific embodiments of more general claims.